IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:

Yoram SELA

Application No. 10/500,634

Filed: July 2, 2004

EXTENDED RELEASE COMPOSITION COMPRISING AS…

Examiner: Jake Minh Vu
Art Unit: 1618

APPEAL BRIEF

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TABLE OF AUTHORITIES

The present appeal is taken from the final rejection mailed December 8, 2006, of claims 1-7, 9, 10, 12-20, 22, 23 and 25-30. A clean copy of these claims, double spaced, appears in the appendix to this brief.

REAL PARTY IN INTEREST

The assignee of the subject application is LYCORED LTD., P.O. Box 320 BEER-SHEVA, ISRAEL 84102. The assignment was recorded in the U.S. Patent and Trademark Office on July 3, 2006, under Reel 017871, Frame 0733.

RELATED APPEALS AND INTERFERENCES

There are no known related Appeals or Interferences.

STATUS OF CLAIMS

Claims 1-7, 9, 10, 12-20, 22, 23 and 25-30 are rejected.

Claims 8, 11, 21 and 24 are cancelled.

STATUS OF AMENDMENTS

All amendments have been entered. Paragraph 7 of the Advisory Action mailed May 17, 2007, explicitly states that the amendment in reply to the final rejection "will be entered" for purposes of Appeal.

SUMMARY OF CLAIMED SUBJECT MATTER

The present application contains two independent claims, namely claims 1 and 29. Both of these claims, indeed all the claims in the application, call for an extended release dosage form of Venlafaxine hydrochloride, a highly water-soluble antidepressant (see page 1 of appellant's specification), comprising a nonpareil inert core, a first coating over the core of the active agent Venlafaxine hydrochloride, a second coating over the active agent comprising a hydrophilic or water soluble polymeric layer which provides an isolating, protecting and/or separating function, and a third coating comprising a hydrophobic polymer which provides a controlled release function.

I-Claim 1

An extended release composition: The first paragraph of appellant's specification states that the present invention relates to extended release compositions comprising Venlafaxine hydrochloride as the active compound.

The active compound Venlafaxine hydrochloride is coated on a nonpareil inert core. Support is found in the penultimate paragraph on page 3 of appellant's specification and elsewhere, including the last line on page 3.

The so-coated core is coated with an isolating layer comprising a hydrophilic or water-soluble polymer which

provides at least one function of isolating, protecting and separating [the Venlafaxine hydrochloride layer from the upper layer], support being found in the sixth paragraph on page 4 of appellant's specification, i.e. "the coated core is coated with an isolating/protecting/separating layer" formed of a hydrophilic or water soluble polymer, those exemplified being polyvinyl-pyrrolidone, hydroxypropylcellulose, hydroxypropyl-methylcellulose, microcrystallinecellulose, carrageenan, GMS, etc.

The aforementioned second coating is then coated with a controlled release polymeric layer which enable the controlled release of the Venlafaxine hydrochloride over an extended time. Support is found for example in the seventh paragraph on page 4 of appellant's specification which indicates that the isolating layer (the second aforementioned layer) "is coated then with an additional polymeric layer which enables the controlled release of Venlafaxine hydrochloride."

II-Claim 29

Claim 29 call for the same product as claim 1, as described above, using somewhat different language and adding some additional detail.

Thus, the Venlafaxine hydrochloride layer is stated to be present in an amount of 30-60% based on the total weight

of the dosage form composition, support being found in lines 3 and 4 on page 4 of appellant's specification.

The second layer which performs the function of isolating/protecting/separating is recited as comprising 0.5-10% of the total dosage form, support being found at page 4, last sentence of sixth paragraph of appellant's specification.

The third or controlled release layer is recited as comprising 2-15% of the total dosage form, support being found in the bottom paragraph on page 4 of appellant's specification. Appellant has noticed a clerical error in claim 29 in the sixth paragraph, first line: after the first "said", reference should be made to the preceding (second) polymeric layer.

Claim 29 ends with a means clause which specifies that the control release layer (the third layer) constitutes "means to control release of the Venlafaxine hydrochloride over an approximately 24 hour period." That the third layer enables the controlled release of Venlafaxine hydrochloride is stated in the first sentence of the seventh paragraph on page 4 of appellant's specification. As regards the release time of 24 hours, this is implicit in appellant's specification from the text at page 2, fifth paragraph and the table on page 3, together with the second sentence under the table on page 3

which states that the present invention provides an alternative once daily bioequivalent formulation.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There is only one rejection. All the claims are rejected under §103 as obvious from Jeary et al WO 00/71099 (Jeary) in view of McTeigue et al USP 6,149,943 (McTeigue) and Kamada USP 5,505,983 (Kamada).

ARGUMENT

Appellant respectfully maintains that the proposed combination, even if it were obvious, would not result in the claimed subject matter. The prior art does not disclose or teach or give any reason for the provision of an intermediate layer between the active agent layer and the upper layer.

I-WHAT THE PRIOR ART DISCLOSES

Jeary, the main reference, was originally applied as a tertiary reference in a rejection which was subsequently withdrawn. It relates to controlled release pharmaceutical formulations for oral administration, and in particular controlled release forms of fluvoxamine (Luvox) which, unlike Venlafaxine HCL, is only sparingly soluble in water. In its considerable disclosure (it runs 63 pages, not including drawings) it mentions other compounds of similar activity, sometimes referred to as "Selective Serotonin Reuptake Inhibitors" or SSRI compounds, and among these is mentioned Venlafaxine at page 5, line 15, and again in claim 7 among such other compounds of similar activity.

According to Jeary, the dosage form is a pellet comprising a core of the SSRI compound, the core being coated with a rate-controlling polymer. Jeary states in part at the bottom of page 3 and the top of page 4, under the heading "Disclosure of Invention" as follows:

> The [Jeary] invention provides a multi particulate controlled release SSRI formulation for oral administration, which comprises particles of said SSRI… coated with a rate-controlling polymer which allows controlled release of said SSRI over a period of not less than about 12 hours following oral administration.
>
> Preferably, the particles are pellets or beads.
>
> Further, preferably, said pellets comprise a core of said SSRI…coated with said rate-controlling polymer to form a rate-controlling membrane surrounding said core. [bracketed material added]

The rate-controlling polymer forming the rate-controlling membrane comprises a major proportion of a pharmaceutically acceptable film-forming, water-insoluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water-soluble polymer.

Jeary provides no actual experiments with respect to Venlafaxine. All the examples deal with fluvoxamine which, as noted above and indicated in Attachment E to the entered Reply filed April 5, 2007, is only "sparingly soluble in water".

At page 8, lines 16 and 17, Jeary states that the core, namely a powder mixture of the fluvoxamine and a polymeric binder, "can comprise layers of said powder mixture and said polymeric material superimposed one upon the other." This has been interpreted by the examiner as a disclosure of plural and different layers leading the person of ordinary

skill in the art toward appellant's invention. However, the examiner appears to misinterpret the disclosure by Jeary of a polymeric layer composed of Eudragit and a plasticizer (pg. 8, lines 6-17 and pg. 9, lines 16-22) as an additional and different polymeric layer.

But please note the description of the layers comprising this formulation on pg. 8, lines 6-17, of Jeary where Jeary explicitly mentions (pg. 8, line 16-17) that "*the core can comprise layers of said powder mixture and said polymeric material* ***superimposed one upon the other***" [emphasis added]. In other words, there is no additional and different polymeric layer, but instead an **alternating** of the same layers of the powder mixture and polymeric material comprising the formulation.

Hence, there is only in effect one layer of coating on the powder of the active ingredient in Jeary, and no intermediate layer (as claimed by appellant) of a different character to provide the needed isolating, protecting and/or separating function which appellant has discovered is needed when the active agent is the highly water soluble Venlafaxine HCl.

McTeigue discloses a pharmaceutical dosage form in which a seed core comprised predominantly of microcrystalline-cellulose, having an average particle size of about 180µm, is

spray coated with a pharmaceutically active ingredient in solution form (column 1, lines 40-50; also see column 3, line 56 through column 4, line 14).

McTeigue also discloses that if controlled release is desired, the active ingredient layer may be coated with a polymer system, e.g. a mixture of cellulose acetate and EUDRAGIT E 100 (column 4, lines 27-35, and following table). Specific examples 3 and 5 exemplify tablets of this type wherein the active agent layer is coated with, in these cases, a taste masking layer as opposed to a control release layer.

McTeigue contains no disclosure of a three-layer coated core wherein the bottom active agent layer is separated from the uppermost layer by an intermediate layer which performs an isolating, protecting and/or separating function. It appears that McTeigue also exemplifies only water-insoluble or poorly soluble active ingredients.

Kamada is somewhat similar to McTeigue in that it involves pharmacologically inactive spherical seed cores of microcrystalline cellulose. The key point in Kamada, as understood, is that the pharmacologically inactive spherical seed cores must contain at least 50% microcrystalline cellulose having an average degree of polymerization between 60 and 375.

For pharmaceutical preparation, the seed core particles are coated with the active agent and, if necessary, an excipient, and an aqueous binder solution may also be used (paragraph at the bottom of column 4). The so-coated granules may then be coated (column 4, line 65 through column 5, line 7) for sustained release, masking of bitter taste, etc.

As with McTeigue and Jeary, there is no disclosure in Kamada of providing an intermediate layer between the active agent layer and the top layer, and Kamada appears to have nothing to do with rate controlling of highly soluble materials like Venlafaxine hydrochloride.

II-APPELLANTS CLAIMS DEFINE NONOBVIOUS SUBJECT MATTER

Contrary to each of the three references relied upon, and contrary to any possible combination of those three references, the present invention relates to an extended release composition comprising as active compound Venlafaxine HCl, in which the Venlafaxine HCl is coated on a nonpareil inert core with a water soluble binder, which coated core is coated with an intermediate water-soluble polymeric layer. Such intermediate layer or sub-coating is critical because the Venlafaxine hydrochloride tends to influence the stability of the upper coating and must be separated by such sub-coating or intermediate layer.

The intermediate layer or sub-coating, which is sometimes referred to as the isolating layer, is then overcoated with an additional polymeric layer which enables the controlled release of the Venlafaxine HCl. Such additional polymeric layer is composed of a hydrophobic polymer mixed with an appropriate hydrophobic or hydrophilic plasticizer.

In contrast to all three citations, the present invention involves a formulation having a coating of an active ingredient on the core with two layers therebove, the intermediate layer of which comprises water-soluble or hydrophilic polymers.

A key point with respect to the present invention is the relevant solubility in water of Venlafaxine HCl compared with the solubility of most other anti-anxiety/SSRI compounds which are only slightly soluble in water. These other compounds therefore do not present the same stability problems in formulating an extended release dosage form as exists with respect to the very water-soluble Venlafaxine HCl. Because Venlafaxine HCl is so much more soluble in water than other SSRI's, it needs protection to form a suitable controlled release formulation, and this is what the present invention provides by the provision of the intermediate layer, unlike

anything in the prior art or anything which could be gleaned from consideration of the three references together.

The solubility issue is discussed in appellant's specification. At page 1, third paragraph, it is pointed out that Venlafaxine Hydrochloride has a solubility of 572 mg/ml in water, and this is confirmed by attachment A (copy filed with the last Reply) relating to Effexor XR®. The first full paragraph on page 2 of appellant's specification states as follows:

> In some cases, for example with very water soluble active materials and with relatively high doses it is not feasible to produce tablets which enable appropriate control on the drug release. This is the case, for example with Venlafaxine Hydrochloride.

In contrast to Venlafaxine HCl, other anti-anxiety/SSRI's are only slightly soluble in water as evidenced by attachments B through G, copies of which were filed with the last Reply. Of these, Zoloft® is stated to be only "slightly soluble in water" as is Clomid. Citalopram HBr is said to be "sparingly soluble in water", as is Luvox. Others may be slightly more soluble, but are far less soluble than Venlafaxine.

As pointed out above, appellant's formulation comprises three distinct layers on top of the core, and these three layers must differ from one another:

1. A layer of Venlafaxine Hydrochloride, which is coated on a nonpareil inert core with water soluble binder.

2. A layer of water-soluble polymer (which may be or may be not the same polymer as the binder). This isolating/protecting/separating layer (sub-coating or intermediate layer) is essential because the Venlafaxine Hydrochloride tends to influence the stability of the outer coating and should be separated by this outer layer.

3. A layer of hydrophobic polymer mixed with an appropriate hydrophobic or hydrophilic plasticizer (outer coating). This (outer) layer enables the controlled release of venlafaxine hydrochloride.

The sub-layer, i.e. the intermediate layer, which is a hydrophilic or water soluble polymer layer, is very important because the Venlafaxine HCl tends to influence the stability of the outer coating and therefore need to be separated by such sub-coating.

The outer layer comprising hydrophobic polymer is relatively water-insoluble compared with the sub-layer 2.

As pointed out above, the main reference (Jeary) focuses on Fluvoxamine which is a poorly water soluble drug. The person of ordinary skill in the art does not learn how to handle a highly water soluble drug like Venlafaxine HCl from the teachings of Jeary because, if Jeary's teachings are

adopted for Venlafaxine HCl, a successful result will not be achieved. Control of time release of a poorly water soluble drug like Fluvoxamine, the focus of Jeary, is relatively easy compared with the problem of how to control a highly water soluble drug like Venlafaxine HCl.

The subsidiary references would not lead the person of ordinary skill in the art to any modification of Jeary which would bring a modified Jeary to the present invention. As pointed out above, McTeigue exemplifies only the water-insoluble active ingredients, and does not disclose any intermediate layer, and provides the skilled worker with no reason to add any intermediate layer, or what any such layer should be. It would not have been obvious for any person skilled in the art that the water-soluble Venlafaxine Hydrochloride would be controllably released from the system disclosed by McTeigue because the solubility of the Venlafaxine chloride strongly affects the rate of release, and as a result, the choice of coating.

Finally, Kamada describes the rotor process and coating cores in a rotor system, which has nothing to do with any rate controlling of highly soluble materials like Venlafaxine Hydrochloride. Kamada also provides no intermediate layer or any reason for any intermediate layer. Based on Kamada's teaching, it would not have been obvious for

a skilled artesian to prepare formulation suitable for the controlled release of the Venlafaxine Hydrochloride. Furthermore, the choice of coating is not trivial and could not have been learned from either McTeigue or Kamada.

Even if the proposed combination of the three references were obvious, any resultant reconstruction of Jeary in view of McTeigue and Kamada would not reach the claimed subject matter because none of the three provide the claimed intermediate layer or any reason for it.

III-REPLY TO EXAMINER'S ADDITIONAL COMMENTS IN FINAL ACTION AND ADVISORY ACTION

As regards commentary in the final action, appellant respectfully points out that while appellant indeed did discuss each of the references individually, as must be done in order to address the content of each reference, appellant also has attacked the proposed combination as not leading to the present invention, and furthermore as not reaching the present invention.

A consideration of the references together simply would not have led the person of ordinary skill in the art to solve the problem of the highly water soluble Venlafaxine HCl in an extended release formulation by coating the Venlafaxine HCl on a nonpareil core, providing a hydrophilic polymer layer over the Venlafaxine HCl coating, and then providing a control

release polymeric layer comprising hydrophobic materials over the hydrophilic polymer layer.

In the Advisory Action, the examiner says that Jeary teaches that Venlafaxine can be used in the Jeary formulation. However, that is not appellant's formulation. As stated above, none of the three references discloses appellant's critical intermediate layer which is necessary because Venlafaxine HCl is so highly water soluble.

The examiner then says that McTeigue must use water soluble ingredients, with reference to column 3, lines 46-51. This disclosure relates to the spraying of the active agent onto the microcrystalline cellulose core. McTeigue says that the solvent is preferably water, and of course that would be the most preferable solvent if indeed the selected active agent can be dissolved in water, perhaps even to only a limited degree. McTeigue does not say!

However, in the immediately following paragraph (bottom paragraph of column 3, extending to the top part of column 4), McTeigue appears to include suspensions and dispersions in what is meant by "dissolved in a solvent". So water can be the preferred carrier of even non-soluble components. The active agents can be any of pharmaceuticals, minerals, vitamins, nutraceuticals, and a basket disclosure follows at the top of column 4.

There is not the remotest inference of the need for or the use of appellant's claimed intermediate layer when and upper controlled release layer or an upper layer protecting against objectionable taste is applied over the active material.

Appellant believes and respectfully submits that the examiner's commentary in the Advisory Action amounts primarily to merely a series of conclusions, and that the examiner has not met the burden of providing evidence to establish a *prima facie* case of obviousness.

CONCLUSION

Appellant respectfully submits that the examiner has not met the burden of establishing a *prima facie* case of obviousness. Appellant respectfully requests reversal of the rejection.

Respectfully submitted,

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CLAIMS APPENDIX

CLAIMS UNDER APPEAL

1. An extended release composition comprising

as active compound Venlafaxine Hydrochloride, in which Venlafaxine Hydrochloride is coated on a nonpareil inert core,

which coated core is coated with a hydrophilic polymer layer providing at least one function of isolating, protecting and separating, and

the hydrophilic polymer layer is then coated with a controlled release polymeric layer which enables the controlled release of the Venlafaxine Hydrochloride over an extended time period.

2. A composition according to claim 1, wherein the composition comprises 30-60% of Venlafaxine Hydrochloride per weight of the total dosage form.

3. A composition according to 1, wherein the Venlafaxine Hydrochloride is suitably connected to a binder.

4. A composition according to claim 3, wherein the binder is selected from the group consisting of polyvinyl pyrrolidone, hydroxypropylcellulose and hydroxypropylmethylcellulose.

5. A composition according to claim 4, wherein the composition comprises 0.5%-10% of the binder per weight of the total dosage form.

6. A composition according to claim 5, wherein the nonpareil inert core is an inert sugar core or a microcrystalline cellulose core.

7. A composition according to claim 6, which comprises 30-60% of the core per weight of the total dosage form.

9. A composition according to claim 7, wherein the hydrophilic polymer layer is composed of at least one hydrophilic polymer selected from the group consisting of polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose, carrageenan, and GMS.

10. A composition according to claim 9, wherein the hydrophilic polymer layer comprises 0.5-10% of the weight of the total dosage form.

12. A composition according to claim 10, wherein the controlled release polymeric layer is composed of a hydrophobic polymer mixed with an appropriate hydrophobic or hydrophilic plasticizer.

13. A composition according to claim 12, wherein the hydrophobic polymer is selected from the group consisting of Eudragit and a cellulose derivative, and said plasticizer is selected from the group consisting of castor oil, dibutyl sebacate, glyceryl monostearate, diethyl phalate, glyceryl trihepthanoate, and triethyl citrate.

14. A composition according to claim 13, which comprises 2-15% of the hydrophobic polymer per weight of the total dosage form; and 0.1-2% per weight of the hydrophobic plasticizer per weight of the total dosage form.

15. A composition according to 2, wherein the Venlafaxine Hydrochloride is suitably mixed with a binder.

16. A composition according to claim 15, wherein the binder is selected from the group consisting of polyvinyl pyrrolidone, hydroxypropylcellulose and hydroxypropylmethylcellulose.

17. A composition according to claim 16, wherein the composition comprises 0.5%-10% of the binder per weight of the total dosage form.

18. A composition according to claim 3, wherein the composition comprises 0.5%-10% of the binder per weight of the total dosage form.

19. A composition according to claim 1, wherein the nonpareil inert core comprises inert sugar or microcrystalline cellulose.

20. A composition according to claim 1, which comprises 30-60% of the core per weight of the total dosage form.

22. A composition according to claim 20 wherein the hydrophilic polymer layer is composed of a polymer selected from the group consisting of polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose, carrageenan, and GMS.

23. A composition according to claim 8, wherein the hydrophilic polymer layer comprises 0.5-10% of the weight of the total dosage form.

25. A composition according to claim 23, wherein the controlled release polymeric layer is composed of a hydrophobic polymer mixed with an appropriate hydrophobic or hydrophilic plasticizer.

26. A composition according to claim 25, wherein said hydrophobic polymer is Eudragit or a cellulose derivative, and said plasticizer is selected from the group consisting of castor oil, dibutyl sebacate, glyceryl

monostearate, diethyl phalate, glyceryl trihepthanoate, and triethyl citrate.

27. A composition according to claim 26, which comprises 2-15% of the hydrophobic polymer per weight of the total dosage form; and 0.1-2% per weight of the hydrophobic plasticizer per weight of the total dosage form.

28. A composition according to claim 12, which comprises 2-15% of the hydrophobic polymer per weight of the total dosage form; and 0.1-2% per weight of the hydrophobic plasticizer per weight of the total dosage form.

29. An extended release dosage form, comprising

Venlafaxine Hydrochloride in an amount of 30-60% based on the total weight of said dosage form;

said Venlafaxine Hydrochloride being coated on a nonpareil inert core, said nonpareil inert core comprising 30-60% of the total dosage form;

the Venlafaxine Hydrochloride being optionally connected to a binder in a binder amount of 0.5-10% of the total dosage form;

a hydrophilic polymeric layer coating said Venlafaxine Hydrochloride and comprising 0.5-10% of the total dosage form; and

a control release layer coated over said, said control release layer comprising a hydrophobic polymer optionally mixed with a plasticizer, said hydrophobic polymer comprising 2-15% of the total dosage form, and said optional plasticizer when present comprising 0.1-2% of the total dosage form;

said control release layer constituting means to control release of the Venlafaxine Hydrochloride over an approximately 24 hour period.

30. The unit dosage form of claim 29 comprising hydroxypropylmethylcellulose in at least one of said additional polymeric layer, said hydrophilic layer and said optional binder.

EVIDENCE APPENDIX

ATTACHMENTS A THROUGH G

Attached are duplicate copies of the documents filed as attachments A through G with the entered Reply filed April 5, 2007.

RELATED PROCEEDINGS APPENDIX

NONE